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(54) Title: BIOCOMPATIBLE POLYMERS AND METHODS FOR THEIR USE

(57) Abstract

Biocompatible polymers and methods for their use are provided. The subject polymers comprise at least one biodegradable region. In addition, the subject polymers comprise one of the following features: (1) at least three photo–condensable regions; (2) at least one hydrophobic end group; or (2) at least two hydrophilic end groups. The subject polymers and/or products produced therefrom find use in a variety of different applications, such as materials for use in biomedical devices, such as drug delivery vehicles and the like.

BIOCOMPATIBLE POLYMERS AND METHODS FOR THEIR USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This invention is a continuation in part of application serial no. 60/039,261 entitled

5   "Biodegradable Polymers End-Capped with Hydrophobic or Hydrophilic End-Groups and

Medical Applications Thereof" and filed March 3, 1997 and application serial no.

60/037,151 entitled "Photo curable Biodegradable Compositions as Controlled Release

Carriers and Absorbable Wound Dressings" filed February 14, 1997, the disclosures of

which applications are herein incorporated by reference.

10

INTRODUCTION

Field of the Invention

The field of the invention is biodegradable polymers.

Background of the Invention

15   Synthetic biodegradable polymers are synthetic polymers that degrade into non-toxic

products which are readily eliminated by the body following degradation. A variety of

different biodegradable polymers have been developed, including: polylactic acid,

polyanhydrides, polyorthoesters, polyamino acids, polyesters, *e.g.* of α-hydroxy acids, and

the like. By varying the composition of these polymers, *e.g.* by combining two or more

20   different polymers, modifying the polymeric backbone with functional groups, etc.,

polymers of widely varied physical and chemical properties can be obtained.

Biodegradable polymers find use in a variety of different applications, including

therapeutic, pharmaceutical and surgical applications. Applications in which biodegradable

polymers find use include: controlled-release carriers; adhesives and sealers; materials for

25   use in the prevention of post-operative adhesions; controlled drug release and the like.

While a number of different biodegradable polymers have been developed to date, there is continued interest in the development of new biodegradable polymers and the identification of additional applications for their use.

Relevant Literature

U.S. Patents of interest include: 3,670,045; 4,048,256; 4,478,822; 4,804,691; 4,938,763; 4,942,035; 5,019,379; 5,286,398; 5,317,079; 5,384,333; 5,405,617; 5,410,016; 5,462,976; 5,473,103; 5,476,909; 5,529,914; and 5,548,035. Other references of interest include: Barman, et al., *Fifth World Biomaterials*, (May 29-June 2, 1996) Toronto, Canada, Page 272; Baxter, et al., *Polymer* (1988) Vol. 29:1575-1580.; Cammas, Sandrine et al., *Bioconjugate Chem.* (1995) Vol.6, (2):226-230.; Domb, Abraham et al., *Journal of Polymer Science: Part A: Polymer Chemistry* (1990) Vol. 28:973-985.; Domb, Abraham et al., *Journal of Polymer Science: Part A: Polymer Chemistry* (1995) Vol. 33:717-725.; Garrison, Michael et al., *Journal of Controlled Release* (1994) Vol. 31:263-269.; Kaewvichit, S. et al., *J. Pharm. Pharmacol* (1993) Vol. 46:708-713.; Kawaguchi, Seigou et al., *J. Phys. Chem.* (1994) Vol. 98:7891-7898.; Sakellariou, P. et al., *Colloid Polym. Sci.* (1994) Vol. 272:872-875.; Sawhney, Amarpreet et al., *Macromolecules* (1993) Vol. 26, (4) :581-587.; Sawhney, Amarpreet et al., *Journal of Biomedical Materials Research* (1994) Vol. 28:831-838.; Shih, Chung, *Journal of Controlled Release* (1995) Vol. 34:9-15.; Sodergard, A. et al., *Polymer* (1994) Vol. 46:25-30.; Wang, Daike et al., *Eur. Polym. J.* (1993) Vol. 29, (10):1379-1386.; Yamaoka, Tetsuji et al., *Journal of Pharmaceutical Sciences* (1995) Vol. 84, (3):349-354.; Perrin et al., Purification of Laboratory Chemicals," Pergamon Press, Oxford (1980); and Yokoyama, Shoko et al., *Chemistry Letters* (1994) pp. 445-448.

SUMMARY OF THE INVENTION

Synthetic biocompatible polymers comprising at least one biodegradable region, as well as methods for their use, are provided. In addition to the biodegradable region, the subject polymers comprise one of the following features: (1) at least three photo-condensable regions; (2) at least one hydrophobic end-cap; or (3) at least two hydrophilic end-caps. The subject polymers find use in a variety of different applications, including in medical devices, as drug delivery matrices, as encapsulation agents, and the like.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 provides a partial representation of various embodiments of the photo-condensable polymers according to the subject invention.

Fig. 2 provides a partial representation of various embodiments of the hydrophobic
5   end capped polymers according to the subject invention.

Fig. 3 provides a partial representation of various embodiments of the hydrophilic
end capped polymers according to the subject invention.

DETAILED DESCRIPTION OF THE INVENTION

10   Biodegradable polymers and methods for their use are provided. The subject
polymers comprise at least one biodegradable region. In addition, the subject polymers
comprise one of the following features: (1) at least three photo-condensable regions; (2) at
least one hydrophobic end group; or (3) at least two hydrophilic end groups. The subject
polymers, and compositions produced therefrom, find use in a variety of different
15   applications, including in biomedical devices, in drug delivery matrices, as therapeutic
agents, and the like.

Before the subject invention is further described, it is to be understood that the
invention is not limited to the particular embodiments of the invention described below, as
variations of the particular embodiments may be made and still fall within the scope of the
20   appended claims. It is also to be understood that the terminology employed is for the purpose
of describing particular embodiments, and is not intended to be limiting. Instead, the scope
of the present invention will be established by the appended claims.

In this specification and the appended claims, the singular forms "a," "an," and "the"
include plural reference unless the context clearly dictates otherwise. Unless defined
25   otherwise, all technical and scientific terms used herein have the same meaning as
commonly understood to one of ordinary skill in the art to which this invention belongs.

The subject polymers are biocompatible, by which is meant that polymers, as well as
the degradation products thereof, are non-toxic, at least in the amounts in which they are
employed. The subject polymers are heteropolymers, usually block copolymers, and may
30   have a variety of different configurations, including linear and branched configurations,
where the branched configurations may be simple or complex. The molecular weight of the
subject polymers may vary widely depending on their intended use, but will generally be at

least about 400, usually at least about 2000 and more usually at least about 10,000, where the molecular weight of the subject polymers may be as great as 100,000 daltons or greater, but will generally not exceed about 40,000. The subject polymers may or may not be cross-linkable, as described in greater detail below.

5   A common feature of the subject polymers is the presence of at least one biodegradable region. By biodegradable is meant a component that degrades under physiological conditions into non-toxic products, where the biodegradable extension component will generally be hydrolyzable. Hydrolyzable components of interest include: polymers, copolymers and oligomers of: glycolide, dl-lactide, d-lactide, l-lactide,

10   caprolactone, dioxanone and trimethylene carbonate or their copolymers and the like. Illustrative biodegradable regions include: polyhydroxyacids, such as polylactic acid and polyglycolic acid, polyorthocarbonates, polyanhydrides, polylactones, polyaminoacids and polyphosphates and the like. As described in greater detail below, certain combinations of biodegradable and modifying regions are preferred.

15   In addition to having at least one biodegradable region, the subject polymers further include one of the following features which serve to modify the characteristics of the polymers: (1) at least three photo-condensable groups; (2) at least one hydrophobic end-cap; or (3) at least two hydrophilic end caps. Each of these polymeric species will be described in greater detail separately below.

20

Photo-condensable Polymers

In a first embodiment of the invention, the polymers comprise at least three photo-condensable groups in addition to the at least one biodegradable region. The polymers may be a liquid, a solid, a solution or a physical gel. The polymers may or may not be water

25   soluble, or partially water soluble. The polymers of this embodiment are capable of undergoing a chemical cross-linking reaction, preferably upon exposure to electromagnetic radiation, more preferably in the ultraviolet and visible region, particularly in the region between 280 to 800 nm and most preferably around 300 nm, to produce cross linked polymers or macromolecules, as described in greater detail below.

30   The polymers comprise at lest three photo-condensable groups separated by at least one biodegradable region. The term photo-condensable, as well as photo-dimerizable, is used herein to refer to functional groups which react inter-molecularly or intra-molecularly

upon exposure to electromagnetic radiation of appropriated wavelength to form a dimer or analogous adduct. A critical feature of the photo-condensable groups of the subject polymers is that they dimerize or form adducts without the use of a free radical initiator. Representative photo-condensable groups found in the subject polymers include: derivatives

5   of cinnamic acid, coumarin, chalcone and thymine, where cinnamic acid derivatives are preferred functional groups in many, though not all, embodiments of the subject invention. The photo reactive functional groups of the subject polymers may be chemically modified to further tailor their properties for a particular use, where exemplary modifications include addition of water solubilizing groups such as sulfonate, carboxylates or polyalkyleneoxide or

10   polyethylene glycol.

As mentioned above, the polymers of this species comprise at least one biodegradable region, where the number of distinct biodegradable regions of the polymer may be much greater depending on the polymer configuration. The biodegradable regions of the polymers of this embodiment may be hydrophilic or hydrophobic.

15   Although the different regions of the subject polymers may be configured in a variety of different ways, it is preferred that Photo curable regions are located at the ends of hydrolyzable regions, as such a configuration provides control over the cross linking density of a desired photo cured composition. The size or length between the two Photo curable regions can also be varied to control the cross linking density. The degree of cross linking in

20   materials prepared from the polymers of this embodiment, which is defined as the molecular weight between crosslinks, may vary depending on their intended use, but will usually range from about 200 to 20,000, usually from about 500 to 10,000 and more usually from about 1000 to 3000 daltons.

Appropriate selection of specific biodegradable and Photo curable groups can be used

25   to obtain polymers with desirable properties, *i.e.* to tailor the polymers to achieve products with desired chemical and/or physical properties. Thus, the length of biodegradable region can be tailored to achieve precursors with different physical properties, *e.g.* a liquid or solid. For example, an oligomeric copolymer of lactide and caprolactone as a degradable region produces liquid precursors, whereas polyvinyl alcohol based precursors provide a film

30   forming precursor. The biodegradable and photodimerizable region can be chosen such that the precursor polymer is a liquid at certain temperatures, *e.g.* ambient or human body temperature, and a gel at other temperatures, *i.e.* it is thermoreversible. The degradation

behavior of cross-linked materials prepared from the subject polymers can be controlled by choosing different types of biodegradable polymers. For example, polymers with polyglycolic acid based precursors degrade much faster than polycaprolactone. Alternatively, degradable regions may be synthetic polypeptides sequences or polyaminoacids which can

5   be hydrolyzed or cleaved by specific enzymes present inside the human or animal body.

In addition to the biodegradable and photo curable groups, the polymers of this embodiment may also comprise inert polymeric regions which further modulate the resultant chemical and/or physical properties of the polymers and/or cross-linked materials prepared therefrom. Many inert polymers can be used, where some of the preferred examples are

10   polyethylene glycol, polyethyleneoxide, polyethyleneoxide -polypropyleneoxide block copolymers, polyvinyl alcohol, polyvinyl pyrrolidone, dextrans, polyaminoacids, polyethyloxzoline. For example, the polymers can be made water soluble by choosing the appropriate combination of inert and biodegradable regions, e.g. a copolymer of polyalkylene oxide (preferably polyethylene glycol) and polyhydroxyacid (polylacticacid).

15   This can be achieved by choosing a high molecular weight polyethylene glycol (e.g. mol. wt. 10,000 or more) and extending it with a relatively smaller molecular weight oligopolyhydroxy acid (e.g. mol. wt. <500 daltons). Furthermore, the incorporation of polyalkylene oxides most preferably polyethylene glycol or polyethyleneoxide and polyethyleneoxide-polypropyleneoxide block copolymers in the precursor structures

20   incorporates important properties like water absorption or solubility, viscosity of aqueous solution, resistance to protein adsorption, etc to the polymers and/or the cross linked products prepared therefrom.

In certain embodiments, it is desirable to have a colorant agent which provides for visualization of the polymer composition, which may or may not be cross linked. Suitable

25   colorants are agents that are biocompatible, such as pharmaceutically acceptable dyes. The agents may be purchased commercially from any convenient source. One convenient and practical source of a colorant agent is commercially available colored sutures. For example, a colored suture can be cut or ground into fine powder and combined with the polymeric precursor prior to curing.

30   The polymers may have one or more bioactive and/or labeling agents covalently attached or conjugated to them. Bioactive agents of interest include naturally occurring and synthetic molecules, such as proteins, peptides, and fragments thereof, oligosaccharides,

small molecules and the like. Labeling agents include agents used in imaging, such as iodine, and the like.

The subject polymers will now be further described in terms of the representative configurations provided in Fig 1. In these examples, the biodegradable region is represented

5   by (/\/\/\/\). The photo-condensable (PC) or photodimerizable (PD) region is represented by (━━━). In some compositions an inert, biocompatible block may be used to add some additional properties to these structures such as water solubility. The inert block may or may not be biodegradable. This is represented by (——). A bioactive compound or a drug such as paclitaxel or an imaging aid such as triiodobezoiic acid (iodine acts as x-ray

10   imaging aid) can be physically or chemically attached to such the precursors. These are represented by (◈-). Structure A shows a 3 arm biodegradable polymer end-capped with photo-condensable region. Structure B shows a 4 arm biodegradable polymer with PC region at the end. Structure C shows a linear molecule with photo-condensable regions in the backbone and the photo-condensable regions are separated by biodegradable region.

15   Structure D shows a graft type biodegradable polymer substituted with photo-condensable region. Structure E shows a tetra functional biodegradable polymer whose ends groups are partially substituted with photo-condensable groups. The partial substitution permits some control over cross linking density of the photo cured macromolecule. The unsubstituted site may be attached with a drug which is shown in structure F. The photo-condensable regions

20   permit cross linking while the biodegradable regions releases the bioactive compound upon hydrolysis or degradation. Structure G is a tetra functional precursor in which the major component is an inert biologically acceptable polymer such as polyethylene glycol which is placed at the core. The insertion of the inert region imparts water solubility to the precursor. Structure H is similar to structure G where the molecule is multi functional. Structure I is

25   similar to structure H but the photo-crosslinkable regions are partially substituted. Structure J is similar to structure I where biodegradable segments are substituted with photo-crosslinkable region and biologically active component. Structure K is a graft polymer in which the linear portion of the molecule is an inert molecule such as polyvinyl alcohol. The photo-crosslinkable regions are attached at the ends of biodegradable regions. Structure L is

30   a trifunctional precursor in which inert regions are attached to photocondensable regions. The structure J is similar to structure L where a biologically active compound is attached to the photocondensable region. Structure K is a graft copolymer precursor in which

biologically active compound and photo-condensable compounds are attached at the ends of
degradable region.

Cross linked products prepared from the subject polymers are of particular interest.
To cross-link the polymers, a composition of the polymer, generally an aqueous composition

5   or neat liquid is exposed to electromagnetic radiation sufficient to dimerize the photo-
condensable groups of the polymers, e.g. around 280 nm for cinnamate groups and around
320 nm for chalcone groups. Depending the absorption maxima of a given formulation,
conventional light sources such as mercury lamps or xenon lamps with appropriate light
filters to remove short UV and infrared light may be used. As an alternative to mercury

10   lamps, lasers whose wavelength is tuned to emit around the desired curing wavelength may
also be used.

The photocondensation or photodimerization reaction can be sensitized to occur at a
desired wavelength by including an appropriate sensitizing agent. A variety of sensitizing
agents may be employed. The sensitizer may be an organic dye which is suitable for use in

15   medical applications or it may be non-linearly optically active compound (NLQ), meaning
its chromophore yields a second harmonic radiation upon exposure to longer wavelength of
light. For example the dimerization of cinnamic acid derivatives occurs around 280 nm.
Incorporation of NLQ dye which absorbs around 560 nm light and emits around 280 nm
light then initiates dimerization reaction.

20   The properties of the resultant cross linked materials can be modulated by carrying
out the curing reaction in the presence of compounds with only one or two Photo curable
groups which are added to control the cross linking density of the cured structures.

The properties of the resultant cross linked material produced from the subject
polymers can also be modulated by varying the conditions under which the cross linking is

25   carried out. For example, an aqueous polymeric precursor solution can be photo cured to
produce hydrogel structures with variety of physical properties. The photo curing of aqueous
solutions can be carried out at low concentration 2 -10 % to 40-60 % concentration. The
preferred concentration is 10-30%. Depending on the aqueous concentration used during
photo curing, the cross linked structure can absorb large or small amounts of water. This

30   control over water absorption by choosing precursor concentration in water prior to photo
curing is important in some applications such as wound dressings. The aqueous precursors
discussed above based on polyalkyleneoxide and polylactate (PLA) may be chosen to have

thermoreversible physical gelation behavior. For example, polyalkyleneoxide may be Tetronic 908 (a block copolymer of polyethyleneoxide and polypropyleneoxide available from BASF Corporation). This gelation behavior can be maintained or altered by nature and length of biodegradable segment. Aqueous solutions of such precursors can exist as solution,

5   pastes or physical gels depending on the concentration, temperature and chemical composition of the precursor. Some structures in Fig 1 involve partial substitution of photo-crosslinkable regions. This permits better control over cross linking and hence the properties of photo cured structures. In some structures, the photo-crosslinkable regions as well as other medically useful compounds can be substituted at the ends biodegradable polymers. This

10   permits photocrosslinking as well as controlled release of medically useful compounds. If the medically useful compound is an iodine or heavy metal containing molecule then it can serve as marker for x-ray imaging. Other markers that may be useful are Gd containing compounds for nmr imaging. Some radioactive compounds which are useful for diagnostics or cancer treatment can also be used in such applications.

15   The mechanical properties of the resultant photo cured or cross-linked compositions can be further enhanced by adding particulates or fibers to the compositions. For example, a composite of bioresorbable fibers such as fibers of polylacticacid or its copolymers and hydrophobic liquid precursor can be added to the cross-linked composition. Such fiber reinforced composites can be used where high strength biodegradable materials are desired.

20   In one embodiment, an aqueous precursor solution is used to cure in presence of biodegradable fiber mesh. The cured hydrogel is reinforced with bioabsorbable, biocompatible, biodegradable fibers and can be used as implantable wound dressing. In another embodiment, the fiber reinforced hydrogel is used as biodegradable barrier for prevention of postoperative adhesions. The fibers not only provide improved tear resistance

25   to the photo cured hydrogel but also serve as anchoring or fixation points for mechanical fixation. Those skilled in the art will recognize that there are many different types of biodegradable meshes, with different shapes and sizes that can be used to prepare such composites. Hydrophilic fibers such as protein based suture materials or synthetic biodegradable fibers which have hydrophilic coating are preferred in making hydrogel based

30   fiber reinforced composites.

The subject cross linked polymeric materials, i.e. cured products, find use in a variety of different applications, where such uses include: as materials for controlled drug release; as

materials for use in the preparation of surgical devices, such as membranes for the

prevention of surgical adhesion, wound dressings, tissue adhesives and sealants, in wound

healing, as bone wax, in devices for use in tissue regenerations, as biological agent

encapsulation materials, where biological agents include cells, proteins, e.g. enzymes,

5   hormones, other biologically active proteins; and the like. Specific applications of the

polymers of this embodiment are further described in greater detail below.

Surgical or biomedical devices in which the subject cross-linked polymeric materials

find use include fiber mesh reinforced composite structures. Such composite structures find

particular application as wound dressing and related medical devices. Such structures can be

10   prepared using any convenient methodology. For example, a sterile biodegradable fiber

mesh can be fed in a sheet form under a liquid polymer applicator capable of receiving and

applying a sterile filtered uncured polymer liquid or aqueous solution, which applies the

uncured material on the biodegradable fiber mesh in an amount just sufficient to impregnate

the interstices therein. The uncured coated material is then immediately fed to an area where

15   the uncured material is exposed to electromagnetic radiation preferably to UV or visible

radiation with wavelength around 290 nm. Alternatively, one can employ an uncrosslinked

polymer composition that is a solution at cool temperatures but a gel at warm temperatures.

In this process, a sterile hydrophilic release material maintained at 40 °C is fed in a sheet

form under an applicator capable of receiving and applying a sterile filtered cold (0 °C to 15

20   °C) uncured aqueous solution of a polymer. The applicator applies the uncured solution on

the release sheet maintained at 40 °C. The solution is then immediately converted into the

physical gel due to thermoreversible gelation property. This gelation immobilizes the liquid

precursor as soon as it is applied on the surface. The thickness of the gel can be controlled by

application of speed, temperature, amount of liquid material applied and chemical

25   composition of the precursor. The uncured coated material is then immediately fed to an area

where the uncured material is exposed to electromagnetic radiation preferably UV radiation

with wavelength around 280 nm to cure the material. The cured material is fed into another

area for subsequent processing such as packing, terminal sterilization etc. Such processing is

particularly suitable for large scale manufacturing of polyalkylene oxide based wound

30   dressings. The absorptive capacity of the wound dressing can be controlled by the aqueous

concentration of precursor. The flexibility, permeability and other physical properties can be

controlled by controlling the cross linked density of the resultant network.

The photo-crosslinkable materials and compositions prepared therefrom also find use as delivery vehicles for biologically active agents. The term biologically active agent is used in its broadest sense to include: pharmaceutically active agents, e.g. therapeutic agents or drugs, where such agents include small molecules as well as biologically derived agents,

5   such as peptides, proteins, and mimetics thereof, both naturally occurring and synthetic, including those exhibiting the R-G-D motif; as well as other types of biologically active agents, such as insecticides, herbicides and the like.

Of particular interest is the use of the cross linked materials as drug delivery vehicles, where the vehicles can be in a variety of forms, such as particles, sheets, films, microspheres,

10   micelles, implants such as depot matrices, and the like. One way of preparing drug delivery vehicles with the subject polymers is to first disperse or dissolve the drug or biologically active compound in a liquid or solution polymeric precursor. The precursor is then formed into desired shape which may be film, rod, microsphere or any other desired shape or size. The formed shape is then irradiated with light to initiate photo curing reaction. In one

15   embodiment, microspheres are prepared by atomizing the drug/polymer solution into small droplets which are captured in a medium in which the liquid precursor is insoluble, such as mineral oil or water. The captured droplets are then converted to solid particles by irradiating the droplets with light under conditions suitable for photo curing. Such a process is suitable for large scale manufacturing of biodegradable microspheres loaded with drugs. The

20   biodegradable cured compositions described in this invention are especially useful for protein or peptide or polysaccharide based therapeutics. In another variation of this process, the aqueous microspheres are prepared by atomizing the drug/polymer solution into small droplets which are captured into a medium such as liquid nitrogen. The liquid nitrogen is evaporated and the frozen microspheres are resuspended in a medium such as mineral oil or

25   silicone oil where they are prevented from agglomerating. the droplets are then photocrosslinked and recovered. The entire process can be carried out in an aseptic manner, and is especially useful for the preparation of hydrogel microspheres.

The subject polymers also find use in delivery vehicles particularly suited for the controlled release of small molecules with low molecular weight (typically less than 1000

30   g/mole). For example, the drug may be dispersed or dissolved in a hydrophobic liquid precursor, formed into desired shape such as microsphere and then cross linked using photo curing reaction. Alternatively, the small compound may be dissolved in a aqueous surfactant

based precursor, such as Tetronic 908 containing polymer described in the experimental section, and the resultant hydrophobic micelles are then photo cured. In yet another embodiment, the drug may be physically or chemically bound to the ends of biodegradable regions in a precursor polymer, which is cross linked to product a delivery vehicle. In yet

5   another embodiment, the drug may be first encapsulated in a biodegradable microsphere or particle. Current microsphere technology permits one to choose a desired release and biodegradation profile of a given microsphere formulation. Such drug loaded microspheres are mixed with liquid or aqueous solution precursors. The dispersion is then photo cured using electromagnetic radiation to a desired shape such film, rods, sheet, spheres etc. In

10   some embodiments, the biodegradable microspheres can be loaded with coloring agent, x-ray, sonography, nmr contrast agents or radioactive agents and then entrapped in a photo cured material.

The subject polymers can also be used to produce wound dressings that comprise one or more blood derived components, such as nutrients, cellular waste products, oxygen,

15   growth factors and the like. To prepare such wound dressings, the polymer may be combined with the agents to be incorporated in the wound dressing, shaped as desired, and then cross linked. For example, the polymer may be combined with whole blood or fractions thereof, such as serum, where the blood may be derived from the person with which the wound dressing is to be used or from a donor source. Where it is desired for the wound dressing to

20   comprise growth factors, cross linking may be done in the presence of platelets, which may be activated to release growth factors either before or after cross linking. In this embodiment, polyoxyalkylene, preferably polyethylene glycol based polymers are preferred.

The subject polymers also find use as encapsulation materials, or materials for tissue engineering applications, particularly for biological agents, such as cells, enzymes, and the

25   like. For cell encapsulation, a cell suspension and aqueous precursor are mixed and then charged into a syringe with 22 gauge needle. The mixture is forced out from the syringe and immediately captured in a beaker containing mineral oil. The beaker is also irradiated with long wavelength UV light for photocrosslinking of the precursor. The process can be easily scaled up for large scale manufacturing using methods known to those of skill in the art. The

30   cross linked hydrogel microspheres containing cells are recovered and used for therapeutic application. In another cell encapsulation process, the ability of the some precursors to form thermoreversible gelation is exploited. In this method, a cold precursor solution (typically

around 0-15 °C) which shows thermoreversible gelation property (physical gelation around
20-45 °C, most preferably at 37 °C) is mixed with cell suspension. The temperature of the
mixture is maintained around 10 °C to prevent physical gelation of the mixture. The mixture
is added dropwise into PBS solution maintained at 37 °C. The temperature causes physical

5   gelation of droplets which prevents its agglomeration. The physically gelled material is
_irradiated with long UV to induce chemical cross linking. In a variation of this process, the
thermoreversible formulation is atomized into droplets which are collected in liquid nitrogen.
The rapid cooling of the liquid nitrogen preserves the droplet shape. The liquid nitrogen is
evaporated and the solidified droplets are transferred into PBS maintained at 37°C and

10   photocured. The higher temperature prevents agglomeration during the photocuring process.
This process is particularly suitable for enzymes and protein based therapeutics.

While being described in terms of the photocondensable polymers of the subject
invention, the above inventive method of producing particles, e.g. microspheres, comprising
an active agent, e.g. a drug, is suitable for use with other types of cross-linkable polymers.

15   Thus, a general method is provided for produce particles comrising an active agent. In this
general method, the active agent, such as a drug or other compound of interest, is combined
with a matrix material comprising a cross-linkable polymer. Particles are then produced from
the matrix, e.g. through atomization of the matrix to produce droplets. The droplets are then
cured through crosslinking of the polymer in the matrix, where the crosslinking or curing

20   may be initiated a number of different ways, depending on the nature of the crosllinkable
polymer. To maintain the shape of the particles prior to curing, the particles may be frozen
by reducing the temperature of the particles, where a convenient means of freezing the
particles is by immersion in liquid nitrogen.

Photocurable compositions discussed in this invention are especially useful in

25   minimally invasive surgical applications where materials/compositions are transported to a
given site using an instrument such as a laproscope. The hydrophobic liquid precursors,
along with biologically active compounds or aqueous solutions can be easily transported
using instruments such as a laproscope. Such compositions are then cured using
electromagnetic radiation. The cured solids degrade into non-toxic products upon hydrolysis.

30   Such in situ formed implants are useful in a variety of surgical applications such as localized
drug delivery, prevention of post-operative adhesions and the like.

Polymers end capped with hydrophobic groups

        In a second embodiment of the subject invention, polymers end-capped with
hydrophobic groups are provided. The biodegradable polymers of this second embodiment
may be liquid, solid, semi-solid or wax type materials. The biodegradable polymer may be
5   completely water soluble or insoluble, as well as partially soluble. The polymers of this
second embodiment are heteropolymers, usually block copolymers, which may be linear or
branched, where the branched configurations may be relatively simple or complex. Though
varying greatly depending on their intended use, they will generally have a molecular weight
of at least about 200, usually at least about 5000 and more usually at least about 15000,
10   where the weight may be as great as 500,000 daltons or greater.

        The biodegradable region of the polymers of this embodiment may be hydrophilic or
hydrophobic, as described above. In this embodiment, preferred biodegradable polymers are:
poly(lactic acid) or poly(lactide), polyhydroxy acids, polylactones, polycaprolactones, and
poly(glycolic acid) or poly(glycolate), as well as copolymers thereof, while polyanhydrides
15   are less preferred.

        In addition to the biodegradable region, the subject polymers of this second
embodiment further comprise at least one hydrophobic end group, where generally all of the
ends of the subject polymers will be capped or terminated with a hydrophobic end group.
Hydrophobic end groups finding use will generally be relatively long alkyl chains, as found
20   in naturally occurring fatty acids, where the chains will generally be from 6 to 22 carbon
atoms in length and may comprise one or more sites of unsaturation. Preferred alkyl chains
serving as the hydrophobic end group of the subject polymers are those chains found in
naturally occurring fatty acids, including: caproic, arachidic, caprylic, heneicosanoic,
heptadecanoic, heptanoic, lignoceric, nonanioc, nonadecanoic, pentadecanoic, tricosanoic,
25   tridecanoic, undecanoic, petriselinic, docosahexanoic, erucic, linolenic, elaidic, linoleic,
nervonic, behenic, palmitoleic, arachidonic and oleic and the like. In some instances, the
hydrophobic end groups may be 6-22 fluorocarbon chains.

        In addition to the biodegradable and hydrophobic end cap components, the subject
polymers may comprise additional regions or domains that further modulate the chemical or
30   physical properties of the polymers in desirable ways. For example, many inert polymers can
be used to modulate the properties of the polymers and/or products prepared therefrom, e.g.
enhance water solubility, where some of the preferred examples are polyethylene glycol,

polyethyleneoxide, polyethyleneoxide -polypropyleneoxide block copolymers, polyvinyl alcohol, polyvinyl pyrrolidone, polyaminoacids, polyethyloxzoline and dextran.

Turning now to the figures, representative examples of structures are given in Fig 2. The biodegradable region is represented by (∧∧∧). The hydrophobic end-group is
5   represented by (▬▬). In some compositions, an inert, biocompatible block which is easily cleared by the human body such as polyethylene glycol may be used to add some additional properties to these structures such as water solubility or thermal sensitivity. Inert block may or may not be biodegradable. This is represented by (——). A bioactive compound or a drug such as paclitaxel or an imaging aid such as triiodobezoiic acid (iodine acts as x-ray imaging
10   aid) can be physically or chemically attached to such the polymers. These are represented by (◈▬). Structure A shows a linear biodegradable polymer end-capped with one HPEG such as fatty-acid. Structure B shows linear biodegradable polymer end-capped two HPEG. Structure C shows, a branched or star shaped biodegradable polymer terminated with HPEG. Structure D shows a multibranched star shaped biodegradable polymer whose ends groups are
15   substituted with HPEGs. The structure E shows a graft type biodegradable polymer substituted with HPEG. Structure F shows a multi functional biodegradable polymer whose ends groups are partially substituted with hydrophobic end-groups. The partial substitution sometimes is desirable to obtain suitable polymer properties. The unsubstituted site such as shown in structure F may be attached with a drug which is shown in structure G. The HPEG
20   influences properties like degradation profile, solubility and melting characteristics, while the biodegradable regions release the bioactive compound upon hydrolysis or degradation. Structure H is tetra functional polymer in which the major component is an inert biologically acceptable polymer such as polyether or PEO-PPO-PEO type block copolymer such as Tetronic 908. The insertion of the inert region imparts water solubility or thermal sensitivity
25   to the polymer. The HPEG in structure H is a separated from the inert polymer by small oligomeric biodegradable region such as polylacticacid. Structure I is graft polymer in which the liner portion of the molecule is an inert molecule such as polyvinyl alcohol.

The subject polymers can be obtained using a variety of different synthetic methods, where the particular method will be chosen on the basis of convenience. For example, the
30   polymer described in structure A can be obtained by ring opening polymerization of dl-lactide initiated by a monohydroxy compound such as octanol in presence of suitable catalyst such as stannous octoate. The resultant biodegradable polymer comprising

functional end groups is then contacted with a hydrophobic group functionalized to covalently bond to the end of the polymer upon contact under appropriate conditions. Suitable hydrophobic functionalized end groups include organic hydrophobic functional groups such as long chain aliphatic alcohols, fluorocarbon alcohols, naturally occurring fatty acids, and the like, where naturally occurring fatty acids are preferred.

The physical and/or chemical nature of the resulting polymers and/or products derived therefrom can be modulated by selecting the appropriate end-capping agent and/or biodegradable region. Thus, by selecting a short chain fatty acid (C6 - C12), one end group per chain and relatively high molecular weight biodegradable polymer such polylacticacid, a biodegradable polymer with minimal effect on the bulk and surface properties can be obtained. By selecting long chain fatty acid chains and multifunctional low molecular weight biodegradable regions, a polymer which is predominantly rich in fatty acid content may be obtained. Thus, by varying the type of fatty acid, number of fatty acid molecules per polymer and molecular weight of the biodegradable region, polymers with different fatty acid content may be obtained. The fatty acid content may vary depending upon the intended use, where the content will usually range from 0.01 to 80 %,. For high molecular weight polymers, it may vary from 0.01 to 0.5 %. For low molecular weight polymers, it may vary from about 5 to 80, usually from about 10 to 40 and more usually from about 20 to 30 %. Long chain saturated fatty acids (C12 - C22) are useful in modification of thermoreversible gelation properties of PEO-PPO-PEO-hydroxyacid copolymers. Use of unsaturated fatty acids can provide liquid biodegradable polymers or polymers with low melting point. Furthermore, the incorporation of long chain fatty acids, such as stearic acid, into biodegradable polymers like polyhydroxy acids changes the hydrophobicity of the polymers, decreases the degradation rate of a biodegradable polymer, blocks or prevents the reactive functional group to take part in any undesirable physical or chemical interactions, and modifies, e.g. reduces, the melting point of the polymer and modulates the crystallinity of the polymer.

Biodegradable polymers end-capped with hydrophilic end groups

As with the biodegradable polymers end-capped with hydrophobic groups, the polymers of this third embodiment are heteropolymers, usually block copolymers, where the polymers may be linear or branched, where branched configurations may be simple or complex. The molecular weight of these polymers will generally be at least about 1000,

usually at least about 2000 and more usually at least about 10000, and may be a great as 100000 daltons or greater.

　　　　The biodegradable polymers of this third embodiment will comprise at least one biodegradable region and at least two hydrophilic end groups. The biodegradable region of

5　　the polymers may be as described above, where preferred biodegradable polymers are hydrophobic.

　　　　Hydrophilic end groups of the subject polymers of this embodiment are those groups which are generally water soluble. The preferred hydrophilic end-groups that can be used in end-capping are: polyethyleneoxide, polyethylene glycol, polyethyleneoxide -

10　polypropyleneoxide block copolymers, polyvinyl alcohol, polyvinyl pyrrolidone, polyaminoacids, polyethyloxzoline, cyclodextrans, and the like.

　　　　Partial structures of polymers end-capped with hydrophilic end groups are schematically shown in Fig. 3. The biodegradable region is represented by ($\wedge\wedge\wedge$). The hydrophilic end-group is represented by (ꟷꟷꟷꟷ). In some compositions, an inert,

15　biocompatible block which is easily cleared by the human body such as polyethylene glycol may be used to add some additional properties to these structures such as water solubility or thermo sensitivity. Inert block may or may not be biodegradable. This is represented by (——). A bioactive compound or a drug such as paclitaxel or an imaging aid such as triiodobezoiic acid (iodine acts as x-ray imaging aid) can be physically or chemically

20　attached to such polymers. These are represented by (◈-). Structure A, represents a linear biodegradable polymer end-capped with hydrophilic polymer such as polyethylene oxide. Structure B represents a 3 arm star shaped biodegradable polymer end-capped with hydrophilic groups. Stricture C shows a multiarmed star or branched polymers whose end groups are capped with hydrophilic polymers. Structure D shows a graft polymers on which

25　the hydrophilic polymeric chains are grafted. Structure E represents a multiarm star or branched biodegradable polymer whose ends are partially end-capped with hydrophilic polymers. Structure E is tetra functional precursor in which the major component is an inert biologically acceptable polymer such as PEO-PPO-PEO type block copolymer, e.g. Tetronic 908. Structure F is similar to structure E, where the free end-caps are occupied by a bioactive

30　molecule like drug. This polymer is extended with a biodegradable polymer which is then terminated with hydrophilic polymer. The Structure F is graft type biodegradable polymer partially end-capped with hydrophilic groups. PEO can be incorporated in the biodegradable

polymers using methods like ethoxylation or ethylene oxide polymerization. PEO also can be incorporated using chemically activated (PEO having reactive functional groups) PEO or PEG.

5   A number of different methods, as shown in the experimental section, can be used to prepare the subject polymers. In preparing the subject polymers, building blocks can be chosen to tailor the resultant chemical and/or physical properties of the polymers as desired. In other words, by choosing several structural features such as the nature of end group, (hydrophobic or hydrophilic), number of end-groups per polymer chain, the chain length and chemical structure of the end-group, one can obtain polymers with desired characteristics.

10   The biodegradable polymeric segment can also have several structural variables such as molecular weight and molecular weight distribution, the chemical nature the repeating unit of polymer or copolymer, and the nature of end group.

The resultant physical and/or chemical properties of the polymeric compositions can be further modulated by blending two or more compositions and/ or by the inclusion of

15   various modifying agents. For example, antioxidants, plasticizers, coloring agents, fillers and the like may be incorporated into the polymeric compositions to obtain products with desirable physical characteristics.

The polymers of the second and third embodiments may be used in biomedical

20   applications, such as in medical devices, as controlled drug delivery vehicles, and as materials for use in surgical applications, wound healing, bone wax and the like.. As such, the subject polymers find use as coatings for surgical implants, such as fibers, filaments, sutures and the like, as materials for use as scaffolds in tissue regeneration, as fibers, films, moldings and laminates in medical devices, as plasticizers in the preparation of medical

25   devices, and the like. Surgical operations in which the subject polymers find use include as materials for the prevention of post operative lesions, and the like. Of particular interest is the use of the subject materials in drug delivery, where the polymeric materials may find use as drug particle coatings, as matrices that serve as a depot reservoir for the active agent, and the like, where the drug may be present in crystallized form, as a salt, and the like. Of

30   interest in many embodiments is the use of polymeric compositions in which the polymer is a liquid at room temperature and gels at body temperature, such that it may be administered in liquid form and then gels into a custom tailored shape in situ.

The polymers of the second and third embodiments are especially useful in surgical applications, especially in minimally invasive surgical applications. These polymers can be formulated into liquid or low melting point solids which can be delivered to a surgical site using a simple device such as a syringe or laproscope. For example, a low melting point

5   polymer (melting range just above body temperature, 40 to 70 °C, usually around 45 to 55 °C) is melted in a syringe. The melted polymer is then immediately filled into the body cavity, such as a cavity resulting from tooth extraction or a periodontal cavity. The liquid polymer solidifies in situ conforming to the shape of the body cavity. If desired, the polymer may be mixed with a biologically active compound for enhanced therapeutic effect.

10

The following examples are offered by way of illustration and not by way of limitation.

EXPERIMENTAL

15   I.   **Photo-condensable polymers and representative applications for the use thereof**

Materials and Equipment

Polyethylene glycol is purchased form Sherewater Chemicals, Union Carbide, Fluka and Polysciences. Pluronic® and Tetronic® series polyols are purchased from BASF

20   corporation. DL-lactide, glycolide, caprolactone and trimethylene carbonate are obtained from commercial sources like Purac, DuPont, Polysciences, Aldrich, Fluka, Medisorb, Wako and Boehringer Ingelheim. All other reagents, solvents are of reagent grade and are purchased from commercial sources such as Polysciences, Fluka, Aldrich and Sigma. Most of the reagents/solvents are purified/dried using standard laboratory procedures such as

25   described Perrin et al., supra. Small laboratory equipment and medical supplies are purchased from Fisher or Cole-Parmer.

General Analysis

Chemical analysis for the synthesized polymers includes structural determination using

30   nuclear magnetic resonance (proton and carbon-13), infrared spectroscopy, high pressure liquid chromatography and gel permeation chromatography (for molecular weight determination). Thermal characterization such as melting point and glass transition

temperature is done by differential scanning calorimetric analysis. The aqueous solution properties such as micelle formation, gel formation can be determined by fluorescence spectroscopy, UV-visible spectroscopy and laser light scattering instruments.

5   In vitro degradation of the polymers is followed gravimetriacllly at 37 °C, in aqueous buffered medium such as phosphate buffered saline (pH 7.2). In vivo biocompatibility and - degradation life times are assessed by injecting a sterile, low melting, polymer melt (temperature 40-50 °C) directly into peritoneal cavity of a rat or rabbit or subcutaneously and observing the degradation over a period of 2 days to 12 months. Alternatively, the

10   degradation can be assessed by prefabricated sterile implant made by process like by injection molding or solution casting. The implant is then surgically inserted inside the animal body. The degradation of the implant over a time period is monitored gravimetrically or by chemical analysis. The biocompatibility of the implant can be assessed by standard histological techniques. Wherever necessary, sterile handling techniques must be used, as is

15   known in the art.

Example 1

Preparation of cinnamate derivative of polyoxyalkylene oxide (Tetronic 1307)

30 g of Tetronic is dissolved in 400 ml dry toluene. About 100 ml of toluene is distilled to

20   remove traces of water from the reaction mixture. The warm solution is cooled to 30 °C. To this warm solution, 2.02 g of triethyl amine (TEA) and 3.35 g of cinnamoyl chloride (CC) are added. The reaction mixture is then refluxed for 1 h and filtered. The product is precipitated by adding the filtrate to 2000 ml dry hexane and filtration. It is then dried under vacuum for 12 h at 50 °C. Simmilarly, polyethylene glcyol (molecular weight 10,000, 8

25   hydroxyl groups per chain; obtained from Sherewater Polymers Inc.) is reacted with 4.3 grams of TEA and 12.0 grams CC to obtain a cinnamate terminated polyethylene glycol. Aqueous solutions of the resultant polyaklylene oxide based photocurable derivatives are useful in cell encapsulation applications.

30   **Example 2**

Preparation of multifunctional polylactic acid polymer terminated with cinnamate group

Part 1: Preparation of xylitol lactate

2 g of xylitol, 18.9 g of dl-lactide and 30 mg of stannous octoate are charged in a 100 ml glass sealing tube. The tube is then sealed under argon atmosphere. The sealed tube is then heated in silicone oil bath maintained at 160 °C. The contents of the tube are manually shaken for every 10 minutes. At the end of the reaction, the tube is cooled to room

5   temperature and the xylitol lactate is isolated by braking the glass tube. The polymer is further purified by precipitation from toluene-hexane solvent-nonsolvent system. It is dried overnight under vacuum at 60 °C.

Part 2: End capping of xylitol lactate with cinnamate groups

10   20 g of xylitol lactate is dissolved in 300 ml dry toluene. About 30 ml of toluene is distilled off from the solution to remove the traces of moisture absorbed during the previous synthesis workup. The mixture is cooled to 0 - 30 °C and 19.09 g of triethylamine and 31.5 g of cinnamoyl chloride are added to the solution. The reaction is then refluxed for 6 h under argon atmosphere. The triethylamine hydrochloride is removed by filtration from the

15   reaction mixture. The polymer is isolated by adding the filtrate to large excess hexane. The polymer is purified by precipitation from toluene-hexane system. Alternatively the polymer can be purified by standard chromatographic systems using toluene as solvent and alumina or silica as column packing material.

20   The hydrophobic low melting point solid/liquid polylactic based photocurable precursors produced above are useful in the preparation of drug load microspheres and as matrices for the preparation of fiber reinforced matrix materials.

Example 3

25   Oligomeric photocurable liquid/low melting polymeric precursor:

Part 1: Preparation of trifunctional caprolactone-lactate liquid copolymer

Trimethylolpropane (TMP) is dried at 60 °C overnight under vacuum prior to use. 2 g of dry TMP, 6.6 g of dl-lactide, 10.2 g of caprolactone and 20 mg of stannous octoate are charged into a 3 necked flask equipped with Teflon coated magnetic stirring needle and nitrogen

30   inlet. The flask is then immersed into silicone oil bath maintained at 180 °C. The reaction is carried out for 5 h under nitrogen atmosphere. The reaction mixture is then cooled to room temperature. The mixture is then dissolved in 100 ml toluene. The hydroxy terminated liquid

lactate polymer is isolated by pouring the toluene solution in large excess cold hexane. It is further purified by repeated dissolution-precipitation process from toluene-hexane solvent-nonsolvent system and dried under vacuum at 60 °C. It is then immediately used for cinnamate end capping reaction mentioned below:

5

Part 2: End capping of trifunctional polymer with cinnamate group

25 g of TMP initiated lactate is dissolved in 300 ml dry benzene and 22 g of triethyl amine. The solution is cooled to 0 °C in ice bath. 37.5 g of cinnamoyl chloride is added dropwise to the cold lactate solution . The mixture is stirred under nitrogen atmosphere for 3 days. The

10   solution is filtered to remove triethylamine hydrochloride. The cinnamate ester is then isolated by pouring the filtered solution in large excess cold hexane. It is further purified by repeated (3 times) precipitation from toluene-cold hexane system. The liquid polymer is dried under vacuum at 40 °C. It is stored in amber colored bottle under nitrogen atmosphere.

15   The trifunctional hydrophobic liquid precursors produced above in which the degradation region is composed of a copolymer of caprolactone and lactide are slow degrading. This or other similar liquid precursors can be directly injected in situ in a surgical site and cured in situ. These compositions are thus useful for local controlled drug delivery applications, and for the formulation of tissue conformational implants.

20

Example 4

Synthesis of polyvinyl alcohol-lactate-cinnamate

Part 1: Synthesis of polyvinyl alcohol graft polylactate:

In a 3 neck flask equipped with mechanical stirrer, nitrogen inlet and distillation condenser,

25   2 grams of polyvinyl alcohol (molecular weight 6000 g/mole) and 20 ml d,l-lactic acid solution (approx. 90 % lactic acid) are charged. The flask is then immersed in a silicone oil bath maintained at 150 °C. Most of the water from the reaction mixture is removed over period of 5 hours by distillation. The remaining water is removed by heating the reaction mixture under vacuum at 180 for 15 h. The reaction mixture is cooled and the product is

30   isolated by braking the flask. The product is dissolved in warm acetone and DMSO mixture (1: 3) and precipitated in large excess of ethanol. The precipitated polymer is isolated by filtration and dried in vacuum for 48 h at 60 °C.

Part 2: Cinnamate derivative of polyvinyl alcohol lactate

A 3 necked flask equipped with magnetic stirrer and nitrogen inlet is charged with 5 g of

PVA-lactate copolymer and 100 ml DMSO. The solution is warmed under nitrogen

atmosphere to 70 °C to dissolve the polymer. The solution is cooled to room temperature and

5   5 g of pyridine and 1.6 g of cinnamoyl chloride are added to the reaction mixture. The

solution is then heated to 75 °C for 3 h to complete the reaction. The solution is then poured

into large excess ethanol to precipitate the cinnamate derivative of polyvinyl- lactate. The

polymer is recovered by filtration. The solid polymer is washed with ethanol to remove

solvent and other low molecular weight products.

10   The above polymers of this example are graft type photocurable precursors.

Example 5

Synthesis of water soluble, tetrafunctional precursor based on polyalkylene oxide

Part 1: Synthesis of polyethylene glycol-trimethylene carbonate polyol

15   30 g of tetrahydroxy polyethylene glycol having a molecular weight 20000 is dried at 90-100

°C in a glass sealing tube. The tube is then cooled and transferred inside an air bag where

3.03 g of trimethylene carbonate and 20 mg of stannous octoate are added to the tube. The

glass tube is then sealed under nitrogen atmosphere and heated with stirring at 155 °C and

maintained at this temperature for 6 h. The polyethylene glycol-polytrimethylene carbonate

20   polymer is cooled and recovered by breaking the glass sealing tube. It is further purified by

several precipitations from toluene-hexane solvent-nonsolvent system.

Part 2: Synthesis of polyethylene glycol-polytrimethylene carbonate cinnamate:

10 g of polyethylene glycol-polytrimethylene carbonate is reacted with 0.9 g of cinnamoyl

25   chloride using 0.55 g of triethyl amine as catalyst using a procedure similar as in example 2.

In a similar manner, other polyethylene glycol derivatives with different molecular weights

can be synthesized.

Example 6

30   Preparation of thermosensitive precursor (biodegradable polymer)

Part 1: Preparation of polyalkyleneoxide copolymer lactate polyol(PCLP)

30 g of Tetronic 908 is charged in a dry 3 neck flask equipped with magnetic stirrer and vacuum inlet. The flask is then heated in a silicone oil bath at 100 °C for 12 h to dry the Tetronic 908. The flask is cooled to room temperature and 2.07 g of lactide and 0.02 g of stannous 2-ethylhexanoate is added to the flask. The flask is heated to 160 °C for 6 h under

5 nitrogen atmosphere. The reaction product is then dissolved in 200 ml dry toluene (warming of toluene accelerates dissolution). The toluene solution is added to 2000 ml dry heptane with constant stirring. The product is isolated by filtration. Further purification is accomplished by precipitation of toluene solution of PCLP in heptane. The product is dried in vacuum at 40.°C and used immediately in the next reaction.

10

Part 2: Preparation of polyalkylene oxide copolymer lactate cinnamate

30 g of Tetronic 908 lactate polyol is dissolved in 400 ml dry toluene. 100 ml of toluene is distilled to remove traces of water from the polyol. The solution is cooled to 60 °C and 1.45 g of triethylamine and 2.40 g of cinnamoyl chloride are added. The reaction mixture is

15 refluxed for 3 h under dry argon atmosphere. It is then cooled and added to 2000 ml hexane to precipitate the polymer. The hexane-toluene mixture is decanted from the precipitated polymer. Further solvent removal is achieved by vacuum drying overnight.

Aqueous solutions of the above polyether based precursor show thermoreversible behaviour.

20 **Example 7**

Photo curing of liquid precursor:

3 drops of liquid cinnamate derivative or their solutions in organic solvents, such as described in examples 2 and 3, is placed between two quartz coverslips. The liquid film is exposed to mercury lamp at preferably at 280 nm wavelength. After 10 to 30 minutes of

25 irradiation, the liquid turned into solid indicating the crosslinking of liquid. The cured solid is insoluble in toluene, hexane, acetone and water indicating the formation of crosslinked network. The curing can also be monitored by monitoring the UV absorption of the cinnamate group which decreases upon irradiation with UV. In a similar manner, aqueous solutions of photocurable precursors described in examples 5 and 6 can be cured using UV

30 light.

Example 8

Photocuring of liquid oligomer with albumin as a model drug and monitoring its release

1 - 3 g of liquid oligomer such as described in Examples 2 or 3 is mixed with 10 mg of

albumin. The dispersion is then charged into 20 ml quartz tube and irradiated by a 400 W

5   high-pressure mercury vapor lamp, kept at distance 15-30 cm. The tube is then filled with 10

ml PBS (pH 7.2) and incubated at 37 °C. The PBS is exchanged periodically and the

concentration of albumin is monitored using Biorad total protein assay reagent. The results

demonstrate that the crosslinked polymeric matrix is suitable for use as a drug delivery

vehicle.

10

Example 9

Photocuring of aqueous solutions into biodegradable mesh to prepare fiber reinforced

hydrogel

5 g of precursor such as described in Example 5 is dissolved in 15 ml phosphate buffer

15   saline. The solution is sterile filtered into 50 ml sterile plastic tube. 10 A 4-0 Vicryl sutures

are hand-woven into a 10 X 10 cm size mesh (units size of mesh is 5 mm X 5 mm). This

mesh is placed into 16 mm plastic tissue culture dish. The sterile precursor solution is then

poured into the mesh and irradiated to UV light for 15 minutes. The biodegradable mesh

reinforced gel is ready for animal implantation. Part of the mesh which is not covered with

20   the gel is used to tie the gel at a surgical site using suture, staple or other mechanical fixation

device. Such composites can be used as biodegradable barriers to prevent post operative

· adhesions.

Example 10

25   Curing of aqueous precursors solution which show thermoresponsive behavior:

5 grams of precursor made from Tetronic 908 (synthesized using a procedure described in·

example 6) is dissolved 15 ml cold distilled water. 0.2 ml of the cold solution (0-10 °C) is

exposed to 250 W high-pressure mercury lamp at a distance of 20 cm for 15 minutes. The

flexible cured gel is insoluble in cold and warm water indicating the crosslinking of the

30   precursor. In an another experiment, 1.0 gram of cold solution is charged into 10 ml glass

vial. The vial is then placed into the water bath maintained at 40 °C. The cold solution is

transformed into a gel (physical gelation). The gel is loose and can be easily deformed and

has a consistency like a thick paste which is unable to flow upon inversion of a tube. On

cooling (0-10 °C) the tube, the physical gel turned into flowable liquid. The physical is gel is

exposed to mercury lamp as to form the chemically crosslinked gel. The photocured gel does

not show reversible gelation after its formation and is insoluble in water at low and high

5   temperature. Such a gel finds use in local controlled drug delivery and body cavity space

filling applications.

Example 11

Prevention of post-operative adhesions using biodegradable hydrogel fiber reinforced

10   composite

Rat Secum Model

Fourteen Sprague Dawley rats with average weight around 260 g are divided into 2 groups, 7

animals in each group. After following the standard procedures for administrating anesthesia,

a midline incision is made on the abdomen and a secum is located in the abdominal cavity.

15   Using standard surgical cotton gauze pad , an injury is made to the secum surface by

abrading the surface of cecum. The approx. area of injury is maintained around 1- 2 sq. cm.

The injury is noticed by some bleeding from the injured surface. A fiber reinforced hydrogel

composite is wrapped around the injured surface. The composite is immobilized by tying a

knot with either itself or by suturing it to abdominal wall. While tying a care is taken to

20   ensure that a hydrogel surface is completely covering the injured cecum surface.

Alternatively, aqueous solutions (PBS, pH 7.2) of polyalkylene oxide based precursors (see

examples 5 and 6) can be applied as liquids on the serum and photocured in situ using long

UV light. 7 animals are treated with gel composite and 7 animals are used as controls which

did not receive any gel composite. The animals are closed after the treatment using sutures

25   and staples, topical antibiotic is applied and the animals are subjected to standard diet and

care as recommended by National Institute of Health. After 14 days the rats are subjected to

CO_2 asphyxiation and scoring of adhesions.

The incisions are reopened and the cecum is observed for the adhesions in the area of injury.

30   The adhesions are scored as the percent injured area involved in adhesion formation with the

surrounding organs and peritoneal wall. The results of treated and control animals are

analyzed using standard statistical methods.

Example 12

Preparation of microsphere loaded hydrogel composite

0.1 to 100 micron size microspheres made from polyhydroxy acid such as polylactic acid,

loaded with 10% albumin as model drug are obtained by using standard microsphere

5   preparation method described in chemical literature. 2 grams of polyethylene glycol based

precursor is dissolved in 6 ml PBS. The solution is then sterile filtered and is mixed with 0.8

g microspheres. The dispersion is then poured into sterile plastic dish and exposed to long

ultraviolet light using 400 W high-pressure mercury lamp to cure the solution. The

microspheres are entrapped in a cured hydrogel matrix. The hydrogel composite is cut into 3

10   mm dia pieces. Each pieces is then charged into 50 ml sterile tube containing PBS. The

albumin released from the microspheres is analyzed over a period of 10 days.

Example 13

Cell encapsulation using aqueous precursor solution

15   5 ml 10-40 % polyakylene oxide based precursor (similar to depicted in examples 1, 5, 6

and 18) in phosphate buffered saline (pH 7.2) is mixed with a cell suspension (approx. 0.5

million cells in 0.2 ml) . The mixture is then charged into a plastic 10 ml syringe with 22

gauge needle. The mixture is forced out form the needle and the droplets are collected in 250

ml beaker containing 100 ml mineral oil. The mineral oil is stirred using a magnetic needle

20   and stirrer while receiving droplets from the syringe. It is also illuminated with long

wavelength UV light while receiving cell containing droplets. The photoirradiation causes

crosslinking of the droplets entrapping the cells inside the crosslinked precursor network.

The beads are recovered by filtration and washed with hexane to remove traces of mineral

oil. They are then transferred into appropriate cell culture medium and stored in incubator to

25   maintain the viability of the cells.

Example 14

Cell encapsulation using thermosensitive aqueous precursor solution

2 grams of precursor made from Tetronic 908 (synthesized using a procedure described in

30   example 6) is dissolved 4 to 6 ml cold PBS solution (pH 7.2). This solution is mixed with the

cell suspension at a temperature around 10 -15 °C. The mixture is then charged into a cold 10

ml syringe with 22 gauge needle. At cold temperature (10 -15 °C), the mixture is liquid in

nature and can be discharged from the needle. The cold mixture is discharged from the syringe and collected into a 250 ml beaker containing phosphate buffered saline maintained at 37 °C. The PBS solution in beaker is irradiated with long UV light while receiving the droplets. The temperature of the PBS solution causes physical gelation which prevents

5 agglomeration of droplets in PBS while irradiation causes the chemical crosslinking. The chemically crosslinked beads are recovered using filtration and transferred into appropriate media for storage and further use.

Example 15

10 Autologus or single donor single donor blood or blood components encapsulated wound dressing

5 ml 10-40 % polyethylene glycol based precursor (similar to depicted in example 5) in phosphate buffered saline (pH 7.2) is sterile filtered into a 25 ml amber colored sterile glass vial. The glass vial is loosely capped with rubber septum and lyophilized or freeze dried. The

15 lyophilized sterile powdered precursor is stored in refrigerator for further use.

15-20 ml of fresh human or animal blood is withdrawn in a standard syringe or similar medical device containing anticoagulant such as heparin or acid citrate buffer. The blood is then centrifuged in order to separate out the blood plasma. The plasma is then removed from

20 the centrifuge tube and transferred into prepolymer lyophilized powder to make a 10-40 % solution of prepolymer in plasma. The plasma prepolymer solution is then transferred into sterile plastic dish using a sterile syringe and needle. The contents of the dish are then exposed to long UV irradiation for 10 minutes to crosslink the precursor. The crosslinked precursor is polyoxyalkylene based hydrogel in which serum components are entrapped

25 inside the hydrogel. The hydrogel is suitable for application over external or internal wounds. In some cases, the hydrogel may be impregnated with platelet activating agent such as thrombin to activate the entrapped platelets inside the hydrogel network. The activated platelets release the platelet derived growth factors. The release profile of these growth factors can be adjusted using appropriate crosslink density of the crosslinked network. In

30 some instances, the platelet activating agent may be added prior to photo curing to achieve the efficient release of the growth factors from the platelets. It is preferred that such a wound dressing is prepared using fresh blood and used immediately.

-28-

Example 16

Preparation of colored crosslinked composites

1 to 4 ,4-0 Vicryl suture fibers are cut into several small pieces (typically 1 mm or less size).
Alternatively the suture may be cold milled at liquid nitrogen temperature to produce a

5   powder. 5 ml 10-30 % polyethylene glycol based precursor (similar to depicted in example
5) in phosphate buffered saline (pH 7.2) is sterile filtered into a 25 ml amber colored sterile
glass vial. The chopped suture pieces are then added to the aqueous solution to make a
dispersion. 2 ml this dispersion is then transported using a syringe into abdominal cavity of a
female rat. The dispersion is then applied on the uterine horns and cured 'in situ' using long

10   UV light as mentioned in previous examples. The photocured material can be easily seen
under normal or laparoscopic conditions.

Example 17

Monitoring the degradation of photocrosslinked polymers

15   A total of 200 mg of precursor solution or liquid precursor is crosslinked by exposing to 400
W mercury lamp as mentioned in previous examples. The crosslinked polymers are then
immersed in 10 ml methylene chloride for one day to remove unreacted precursors. The
crosslinked polymers are then dried in vacuum for 1 day at 40 °C. The dried crosslinked
polymers are then immersed in 10 ml PBS, pH 7.2 and incubated at 37 °C. The weight loss

20   of the crosslinked polymer is monitored gravimetrically at various intervals of time.

Example 18

Synthesis of low molecular weight polyethylene glycol based cinnamate derivative
A 3 neck 150 ml flask equipped with a magnetic stirrer and dry nitrogen inlet is flame dried

25   under nitrogen atmosphere. 10 g of trimethylpropane ethoxylated (molecular weight 1106,
obtained from Aldrich) and 750 ml dry toluene are added into the flask. About 30 ml of
toluene is then distilled to remove traces of moisture from the reaction mixture. 1.32 g of
sodium hydride (60% dispersion in mineral oil) is slowly introduced into the flask. A
hydrogen gas evolution is noticed. After complete elimination of hydrogen gas (usually

30   about 30 minutes) 6.6 g of cinnamyl bromide is added to the reaction mixture. The reaction
is refluxed for 8 h under nitrogen atmosphere and cooled. The cooled solution is filtered and
the filtrate is added to 1000 ml cold hexane to precipitate the ethoxylated derivative. The

precipitated derivative is isolated and dried under vacuum for 24 h. The polyalkylene oxide based precursors of this example have no hydrolyzable bonds. Therefore, these precursors are hydrolytically stable and find use in applications such as cell or enzyme encapsulation.

5   **Example 19**

Preparation of microspheres containing bioactive compounds

4 ml of 10-40% polyethylene glycol based precursor solution (similar to depicted in example 1, 6, 5 and 18) in PBS (pH 7.2) is mixed with albumin solution in PBS (final albumin concentration is 10% weight/volume). The following operation is carried out in a sterile

10   biological hood:

The solution is sterile filtered and charged into 10 ml plastic sterile syringe with 22 gauge needle. An aluminum foil is wrapped around the syringe so as to prevent premature photocrosslinking. The solution is then forced out from the needle and the droplets are collected into a sterile quartz beaker containing 100 ml liquid nitrogen. The liquid nitrogen is

15   allowed to evaporate and the frozen droplets are resuspended in 100 ml sterile mineral oil with constant agitation to prevent agglomeration The droplets are also simultaneously illuminated with ultraviolet light to induce photocrosslinking. Alternatively the frozen droplets may be irradiated with UV light to induce photocrosslinking in solid state. After completion of crosslinking, the

20   microspheres are separated from the mineral oil by filtration. The filtered droplets are washed with hexane to remove traces of mineral oil from its surface. Finally the microspheres are lyophilized for storage and future use. This process can be easily scaled up for large scale manufacturing using methods known to those skilled in the art.

25   **II.   Biodegradable Polymers End-Capped with Hydrophilic or Hydrophobic Groups**

Example 1

Preparation of polycaprolactone end-capped with one fatty acid end-group (PCL-1)

Part 1: Synthesis of polylactic acid (PCL1-1):

30   1.00 g of 1-octanol, 17.5 g of caprolactone and 30 mg of stannous octoate are charged into 100 ml Pyrex pressure sealing tube. The tube is frozen in liquid nitrogen and connected to vacuum line for 10 minutes. The tube is then connected to argon gas line and sealed under

argon. The tube is then immersed in oil bath maintained at 170 °C. The polymerization is carried out for 16 h at 170 °C. The polymer from the tube is recovered by breaking the Pyrex tube. The polymer is then dissolved in 100 ml chloroform and precipitated in 2000 ml cold hexane. The precipitated polymer is recovered by filtration and dried under vacuum for 1 day

5   at 60 °C. It then immediately used in end-capping reaction.

Part 2: End-capping of PCL1-1 with steric acid:

10 g of PCL1-1 is dissolved in 150 ml dry toluene. About 50 ml of toluene is distilled to remove traces of water from the reaction mixture. The warm solution is cooled to 30 °C. To

10   this warm solution, 0.92 g of triethyl amine and 2.75 g of stearoyl chloride are added. The reaction mixture is then refluxed for 6 h and filtered. The product is precipitated by adding the filtrate to 2000 ml cold dry hexane and filtration. It is then dried under vacuum for 26 h at 50 °C.

15   **Example 2**

Preparation of polycaprolactone acid end-capped with two fatty acid end-groups (PCL2-2)

Part 1: Synthesis of polycaprolactone (PCL2-1):

2.0 g of 1,6-hexanediol, 20.0 g of caprolactone and 30 mg of stannous octoate are charged into a 100 ml 2-necked flask. The flask is connected to argon gas line and immersed in oil

20   bath maintained at 170 °C. The reaction is carried out for 16 h at 170 °C under argon atmosphere. The polymer from the flask is recovered by dissolving in 20 ml toluene and precipitating in 2000 ml cold hexane. The precipitated polymer is recovered by filtration and dried under vacuum for 1 day at 60 °C. It then immediately used in next reaction.

25   Part 2: End-capping of polycaprolactone with oleic acid:

10 g of PCL2-1 is dissolved in 150 ml dry toluene. About 50 ml of toluene is distilled to remove traces of water from the reaction mixture. The warm solution is cooled to 30 °C. To this warm solution, 5.1 g of triethyl amine and 15.1 g of oleoyl chloride are added. The reaction mixture is then refluxed for 6 h and filtered. The product is recovered by removing

30   the solvent under vacuum. It is further purified by column chromatography using neutral alumina and THF as solvent.

In a similar manner, polycaprolactone end-capped with two steric acid end groups (PCL-2-2) is prepared. In this step, 10 g of PCL2-1 is reacted with 15.0 g of stearoyl chloride and 5.1 g of triethylamine in toluene.

5   **Example 3**

Preparation of polylactic acid copolymer end-capped with three fatty acid end-groups (PLA - 3)

Part 1: Synthesis of trifunctional polycaprolactone-lactate copolymer:

Trimethylol propane   (TMP) is dried at 60 °C overnight under vacuum prior to use. 2 g of
10   dry TMP, 11.68 g of dl-lactide, 18.48 g of caprolactone and 20 mg of stannous octoate are charged into a 3 necked flask equipped with a Teflon coated magnetic stirring needle and nitrogen inlet. The flask is then immersed into silicone oil bath maintained at 160 °C. The reaction is carried out for 10 h under nitrogen atmosphere. The reaction mixture is then cooled to room temperature. The mixture is then dissolved in 100 ml toluene. The hydroxy
15   terminated lactate copolymer is isolated by pouring the toluene solution in large 4000 ml cold hexane. It is further purified by repeated dissolution-precipitation process from toluene-hexane solvent-nonsolvent system and dried under vacuum at 60 °C. It is then immediately used for end capping reaction mentioned below:

20   Part 2: End capping of trifunctional polymer with stearoyl chloride:

10 g of TMP initiated lactate copolymer is dissolved in 150 ml dry toluene and 1.45 g of triethyl amine. The solution is cooled to 0 °C in ice bath and 14.33 g of stearoyl chloride is added dropwise to the cold lactate solution . The mixture is refluxed under nitrogen atmosphere for 2 h. The solution is filtered to remove triethylamine hydrochloride. The crude
25   stearic acid ester is then isolated by removing the solvent from the filtrate under vacuum. It is further purified precipitation from acetone-water solvent-nonsolvent system. The polymer is dried under vacuum at 40 °C for 1 day. It is stored in amber colored bottle under nitrogen atmosphere.

30   **Example 4**

Preparation of multifunctional biodegradable polymer end-capped with fatty acid (PLA-4)

Part 1: Preparation of xylitol lactate:

5 g of xylitol, 50 g of dl-lactide and 30 mg of stannous octoate are charged into a 100 ml glass sealing tube. The tube is then sealed under argon atmosphere. The sealed tube is then heated in silicone oil bath maintained at 170 °C. The contents of the tube are manually shaken for every 10 minutes and the reaction is carried for 6 h. At the end of the reaction, the

5   tube is cooled to room temperature and the xylitol lactate is isolated by braking the glass tube. The polymer is further purified by precipitation from toluene-hexane solvent-nonsolvent system. It is dried overnight under vacuum at 60°C.

Part 2: End capping of xylitol lactate with oleolyl chloride:

10   20 g of xylitol lactate is dissolved in 300 ml dry toluene. About 30 ml of toluene is distilled off from the solution to remove the traces of moisture absorbed during the previous synthesis workup. The mixture is cooled to 0 - 30 °C and 12.8 g of triethylamine and 38.2 g of oleolyl chloride are added to the solution dropwise. The reaction is then refluxed for 6 h under argon atmosphere. The triethylamine hydrochloride is removed by filtration from the reaction

15   mixture. The polymer is isolated by adding the filtrate to large excess hexane. The polymer is purified by precipitation from acetone- water solvent- non solvent system. Alternatively the polymer can be purified by standard chromatographic systems using toluene/acetone as solvent and alumina or silica as column packing material.

20

Example 5

Synthesis of polyvinyl alcohol-lactate-stearate (PLA-5)

Part 1: Synthesis of polyvinyl alcohol graft polylactate (PVA-lactate):

In a 250 ml 3 neck flask equipped with mechanical stirrer, nitrogen inlet and distillation

25   condenser, 2 grams of polyvinyl alcohol (molecular weight 6000 Da) and 20 ml d,l-lactic acid solution (approx. 90 % lactic acid content) are charged. The flask is then immersed in a silicone oil bath maintained at 150 °C. Most of the water from the reaction mixture is removed over period of 5 hours by distillation. The remaining water is removed by heating the reaction mixture under vacuum at 180 °C for 15 h. The reaction mixture is cooled and the

30   product is isolated by braking the flask. The product is dissolved in warm acetone and DMSO mixture (1: 3) and precipitated in large excess water. The precipitated polymer is isolated by filtration and dried in vacuum for 48 h at 60 °C.

Part 2: Stearic acid derivative of polyvinyl alcohol lactate:

A 3 necked flask equipped with magnetic stirrer and nitrogen inlet is charged with 5 g of PVA-lactate copolymer and 100 ml DMSO. The solution is warmed under nitrogen atmosphere to 70 °C to dissolve the polymer. The solution is cooled to room temperature and 0.37 g of pyridine and 1.43 g of stearoyl chloride are added to the reaction mixture. The solution is then heated to 75 °C for 3 h to complete the reaction. The solution is then poured into large excess ethanol to precipitate the stearate derivative of PVA- lactate. The polymer is recovered by filtration. The solid polymer is washed with ethanol to remove solvent and other low molecular weight products and dried under vacuum.

Examples 1,2,3,4 and 5 teach different ways to prepare the structures shown in Fig. 2. Some low molecular weight derivatives with 10-50% fatty acid content are liquid or have low melting points. Such low melting solids and liquids can be directly injected inside the human/animal body and are useful for localized controlled drug delivery and drug loaded microsphere preparation.

Example 6

Synthesis of high molecular weight biodegradable polymer end-capped with fatty acid

Part 1: Synthesis of high molecular weight polylactic acid (PLA-6):

0.2 g of hexanediol is charged into Pyrex glass sealing tube. The tube is then cooled and transferred inside an air bag where 50.48 g of dl-lactide and 50 mg of stannous octoate are added to the tube. The glass tube is then sealed under nitrogen atmosphere and heated with stirring at 170 °C and maintained at this temperature for 6 h. The polylacticacid having 2 hydroxyl end-groups is recovered by breaking the glass sealing tube. It is further purified by several precipitations from toluene-hexane solvent-nonsolvent system.

Part 2: End capping of high molecular weight polylactic acid with fatty acid:

10 g of polylacticacid is reacted with 1.81 g of stearoyl chloride and 0. 61 of triethyl amine using a similar procedure as described in example 1.

Example 7

Synthesis of water soluble biodegradable polymer end-capped with fatty acid

Part 1: Preparation of polyalkyleneoxide copolymer lactate polyol (PCLP):

30 g of polyethylene glycol (molecular weight 20,000 (PEG 20,000)) is charged in a dry 3

neck flask equipped with magnetic stirrer and vacuum inlet. The flask is then heated in a

silicone oil bath at 100 °C for 12 h to dry the PEG 20,000 polymer. The flask is cooled to

5   room temperature and 2.07 g of lactide and 0.02 g of stannous 2-ethylhexanoate is added to

the flask. The flask is then heated to 160 °C for 6 h under nitrogen atmosphere. The reaction

product is then dissolved in 200 ml dry toluene (warming of toluene accelerates dissolution).

The toluene solution is added to 2000 ml dry heptane with constant stirring. The precipitated

product is isolated by filtration. Further purification is accomplished by precipitation of

10   toluene solution of PCLP in heptane. The product is dried in vacuum at 40 °C and used

immediately in the next reaction.

Part 2: End-capping of polyalkyleneoxide lactate copolymer with oleic acid:

20 g of PEG lactate polyol is dissolved in 400 ml dry toluene. 100 ml of toluene is distilled

15   to remove traces of water from the polyol. The solution is cooled to 60 °C and 0.58g

triethylamine and 1.74 g oleoyl chloride are added. The reaction mixture is refluxed for 3 h

under argon atmosphere. It is then cooled and then filtered to removed triethylamine

hydrochloride. The filtrate is then added to 2000 ml hexane to precipitate the polymer. The

hexane-toluene mixture is decanted from the precipitated polymer. Further solvent removal

20   is achieved by vacuum drying overnight at 60 °C. Similarly, other derivatives of

polyethylene glycol with different molecular weights and relatively short regions of

biodegradable blocks and terminated with fatty acid blocks can be made.

Aqueous solutions of the above water soluble fatty acid end-capped polymers form micelles

25   in water (fatty acid and oligomeric hydroxy acid act as hydrophilic groups and PEG acts as a

non-ionic hydrophilic group). These micelles can be loaded with drugs for drug delivery

applications.

Example 8

30   Synthesis of thermoreversible biodegradable polymer end-capped with fatty acid (F108LS)

Part 1: Synthesis of polyethyleneoxide-polypropyleneoxide-polyethyleneoxide lactate

copolymer

Pluronic F108 (polyethyleneoxide-polypropyleneoxide-polyethyleneoxide block copolymer
from BASF) (F108) is dried at 60 °C overnight under vacuum prior to use. 30 g of dry F108,
1.78 g of dl-lactide, and 20 mg of stannous octoate are charged into a 3 necked flask
equipped with Teflon coated magnetic stirring needle and nitrogen inlet. The flask is then

5   immersed into a silicone oil bath maintained at 160 °C. The polymerization reaction is
        carried out at 160 °C for 10 h under nitrogen atmosphere. The reaction mixture is then cooled
        to room temperature and dissolved in 100 ml toluene. The hydroxy terminated lactate
        copolymer is isolated by pouring the toluene solution in 4000 ml cold hexane. It is further
        purified by repeated dissolution-precipitation process from toluene-hexane solvent-

10   nonsolvent system and dried under vacuum at 60 °C. It is then immediately used for end-
        capping reaction mentioned below:

        Part 2: End-capping of polyethylene oxide-polypropyleneoxide-polyethylene oxide lactate
        copolymer with stearoyl chloride.

15   30 g of F108 lactate copolymer is dissolved in 400 ml dry benzene. About 50 ml of benzene
        is distilled off and the solution is cooled to 50 °C. 0.75 g of triethyl amine and 2.27 g of
        stearoyl chloride are added dropwise to the F108- lactate solution . The mixture is refluxed
        for 6 h under nitrogen atmosphere . At the end of 6 h period, the solution cooled and filtered
        to remove triethylamine hydrochloride. The filtrate is added to 4000 ml hexane to precipitate

20   the polymer. It is further purified by repeated (3 times) precipitation from toluene-hexane
        system. The polymer is dried under vacuum at 40 °C. It is stored in amber colored bottle
        under nitrogen atmosphere. This example teaches the use of fatty acid groups to modify the
        thermoreversible gelling behavior of the based polymer. Such polymers find use in
        opthalmic drug delivery.

25

Example 9

Synthesis of biodegradable polymers end-capped with polyalkylene oxide (PLA-9)
Part 1 : Synthesis of hydroxyl group terminated poly(trimethylene carbonate) diol:
3.00 g of hexanediol, 26.82 g of trimethylene carbonate and 30 mg of stannous octoate are

30   charged into 100 ml thick walled Pyrex pressure sealing tube. The tube is then connected to
        argon gas line and sealed under argon. The sealed tube is then immersed in oil bath
        maintained at 160 °C. The reaction is carried out for 16 h at 160 °C. At the end of 16 h

period, the reaction mixture is cooled and the viscous polymer melt is isolated from the tube. The polymer is then dissolved in 30 ml chloroform and precipitated in 2000 ml hexane. The precipitated polymer is recovered by filtration and dried under vacuum for 1 day at 60 °C. It then immediately used in next reaction.

5

Part 2: Ethoxylation of poly(trimethylene carbonate) diol using ethylene oxide:

1 g of hydroxy terminated polytrimethylene carbonate diol is charged into flame dried 250 ml reaction flask. The polymer is then heated to 60 °C under vacuum for 24 h to remove traces of moisture from the polymer. 50 ml anhydrous tetrahydrofuran (THF) is added under

10 nitrogen atmosphere. After complete dissolution of the polymer in THF, 0.35 g of potassium naphthalide is added under nitrogen atmosphere. The reaction flask is then cooled to 0 °C using ice-bath and 22 g of ethylene oxide is added using a cold syringe. The reaction is continued at °C for 72 h under nitrogen atmosphere. At the end of 72 h period, 1 ml water is added to the THF solution and the mixture is stirred for another 1 h. It is then added to 4000

15 ml hexane to precipitate the polymer. The polymer is purified by several precipitations from toluene-hexane solvent non solvent system and dried under vacuum at 60 °C for 24 h.

In a similar manner polylactic acid (molecular weight 1000 Da) end-capped with two PEO chain end-groups (molecular weight approx. 10000 Da, each end) is synthesized.

20

Example 10

Synthesis of monomethoxypolyethylene glycol lactate copolymer

10 g of monomethoxypolyethylene glycol (molecular weight 5000 Da) is dried at 90-100 °C in a glass sealing tube. The tube is then cooled and transferred inside an air bag where 2.02 g

25 of dl-lactide and 10 mg of stannous octoate are added to the tube. The glass tube is then sealed under nitrogen atmosphere and heated with stirring at 170 °C and maintained at this temperature for 6 h. The monomethoxypolyethylene glycol lactate copolymer is recovered by breaking the glass sealing tube. It is further purified by several precipitations from toluene-hexane solvent-nonsolvent system. The purified polymer is dried under vacuum at

30 60 °C for 12 h.

Example 11

Synthesis of monomethoxypolyethylene glycol end-capped with isocyanate group

10 g of monomethoxypolyethylene glycol (molecular weight 5000 Da) is dried under

vacuum at 90-100 °C in a 3 necked reaction flask. 300 ml of toluene, 1.57 g of dry tolylene

5   2,4-diisocyanate and 20 mg of dibutyltindilaurate are charged into the flask. The reaction

mixture is heated to 65 °C for 2 h. The mixture is cooled and charged into a beaker

containing 4000 ml dry hexane. The precipitated polymer is recovered by filtration and dried

under vacuum at 60 °C for 24 h. The polymer is stored under nitrogen atmosphere for future

use.

10

Using a similar procedure, monomethoxypolyethylene glycol (molecular weight 10000 Da)

and monomethoxypolyethylene glycol (molecular weight 400 Da) end-capped with

isocyanate groups are prepared.

15   **Example 12**

Synthesis of monomthoxypolyethylene glycol end-capped with acid chloride group

30 g of monomethoxypolyethylene glycol (molecular weight 5000 Da) is dissolved in 400

ml dry benzene. About 50 ml of benzene is distilled off and the solution is cooled to 50 °C.

3.03 g of triethyl amine and 3.59 g of sebasoyl chloride are added dropwise to the benzene

20   solution. The mixture is refluxed for 6 h under nitrogen atmosphere. At the end of 6 h period,

the solution is cooled and filtered to remove triethylamine hydrochloride. The filtrate is

added to 4000 ml hexane to precipitate the polymer. It is further purified by repeated (3

times) precipitation from toluene-hexane system. The polymer is dried under vacuum at 40

°C. It is stored in amber colored bottle under nitrogen atmosphere.

25

Example 13

Synthesis of high molecular weight biodegradable polymer end-capped with

polyethyleneoxide (water insoluble)

10 g of polylacticacid (hydroxyl group terminated, such as synthesized in example 6) is

30   dissolved in 100 ml toluene. 3.44 g of monomthoxypolyethylene glycol (molecular weight

approx. 400 Da) end-capped with isocyanate group and 20 mg of dibutyltindilaurate are

added to the toluene solution. The reaction mixture is then heated to 65 °C for 2 h. The

mixture is cooled and poured into a beaker containing 4000 ml dry hexane. The precipitated polymer is recovered by filtration and dried under vacuum at 60 °C for 24 h. The polymer is stored under nitrogen atmosphere for future use.

5 **Example 14**

Synthesis of multifunctional biodegradable polymer end-capped with polyethylene oxide

1 g of TMP initiated lactate copolymer (example 3) is dissolved in 150 ml dry toluene. About 50 ml of toluene is distilled from the solution and the solution is cooled to 50 °C. 0.61 g of triethyl amine and 20.51 g of acid chloride activated monomethoxypolyethylene glycol

10 (molecular weight 5000 Da, (example 12) are added to the toluene solution . The mixture is refluxed for 6 h under nitrogen atmosphere. At the end of 6 h period, the solution cooled and filtered to remove triethylamine hydrochloride. The filtrate is added to 4000 ml hexane to precipitate the polymer. It is further purified by repeated (3 times) precipitation from toluene-hexane system. The polymer is dried under vacuum at 40 °C. It is stored in amber

15 colored bottle under nitrogen atmosphere.

Example 15

In vitro release of chlorhexidine diacetate (CHD)from fatty acid end-capped polylacticacid

1.8 g polymer PCL1-2 or similar polymer is dissolved in 10 ml dichloromethane. To this

20 solution 0.20 gram of CHD is added and the solution /dispersion is transferred to 20 ml glass vial. The solvent is evaporated to get the dry loaded polymer matrix. 10 ml PBS are added to the vial. The vial is then kept at 37 °C to monitor the release of CHD. CHD concentration is determined using a UV Vis spectrophotometer HPLC.

25 **Example 16**

Preparation of microparticles using melt method

Fatty acid end capped polymer similar to that as shown in examples 1-3 is heated to approx. 60-95 °C. Acetaminophen, 10% by weight, is added to the heated polymer and mixed. The hot mixture is then sprayed into a container containing liquid nitrogen. The polymeric

30 particles are recovered by evaporating the liquid nitrogen. The acetaminophen release from the particles is monitored at 37 °C using standard HPLC method.

Example 17

Use of water soluble polymer as a carrier of a model drug adriamycin

Water soluble PEG based polymers such as synthesized in examples 7 or 9 are used in this experiment . 1 g of PLA-9 is dissolved in 19 ml of distilled water. This solution is added 5 with 0.2 g of adriamycin. The solution is warmed and dialyzed with 5000 Da cut off dialysis membrane to remove the free drug. The drug solution is then freeze dried to make a solid powder. This freeze dried powder is then used in vitro and in vivo controlled release experiments.

10 **Example 18**

Thermosensitive properties of aqueous solutions of fatty acid end-capped PEO-PPO-PEO-lactate polymer (F108LS) polymer

1 g of F108 LS polymer added into a 50 ml beaker containing 4 ml distilled water. The beaker is immersed into ice bath to form a clear solution of the polymer. 1 ml of this solution 15 is transferred into a cold 5 ml glass vial. The vial is then immersed into a water bath maintained at 10 °C. The vial is inverted to see the gel formation (the gel formation inhibits the ability of the solution to flow upon inversion). The temperature of the bath is increased gradually to 50 °C, at the interval of 1 °C. At each temperature, the ability of the solution to flow is checked. The temperature at which the gelation occurs is recorded. To compare the 20 effect of fatty acid on the gelation temperature, the aqueous solution of Pluronic F108 is used as control. The gel formation of F108LS occurs at lower temperature as compared to control F108 solution when evaluated at the same concentration.

It is evident from the above results and discussion that novel, useful biocompatible, 25 biodegradable polymers and compositions prepared therefrom are provided. Polymers according to the subject invention are capable of being cross linked into materials that biodegrade under physiological conditions into non-toxic low molecular weight products readily eliminated by the body. The cross-linked materials according to the subject invention can be prepared without the use of free radical initiators, making them well suited for use in 30 in vivo applications. The hydrophilic and hydrophobic end-capped polymers of the subject invention overcome difficulties resulting from reactive functional groups present on the ends

of such polymers and provide for desirable chemical and/or physical properties not available with other biodegradable polymers.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1.   A biodegradable polymer comprising:

a biodegradable region; and

one feature selected from the group consisting of: (1) at least three photo-

5   condensable regions; (2) at least one hydrophobic end group; and (3) at least two

hydrophilic end groups.

2.   The biodegradable polymer according to Claim 1, wherein said polymer

comprises at least three photo-condensable regions.

10

3.   The biodegradable polymer according to Claim 2, wherein said photo-condensable

regions are selected from the group consisting of: cinnamic acid, coumarin, chalcone and

thymine.

15   4.   The biodegradable polymer according to Claim 1, wherein said polymer

comprises at least one hydrophobic end group; and further wherein said hydrophobic end

group is a naturally occurring fatty acid.

5.   The biodegradable polymer according to Claim 1, wherein said polymer

20   comprises at least two hydrophilic end groups.

6.   The biodegradable polymer according to Claim 5, wherein said hydrophilic end

groups are polyoxyalkylenes.

25   7.   The biodegradable polymer according to any one of the preceding claims, wherein

the biodegradable region is selected from the group consisting of: polyhydroxyacids,

polyorthocarbonates, polyanhydrides, polylactones, polyaminoacids and polyphosphates.

8.   A composition comprising the biodegradable polymer according to any one of the

30   preceding claims.

9.   The composition according to Claim 8, wherein said composition comprises a biologically active agent.

10.   The composition according to Claims 8 or 9, wherein the biodegradable polymer of said composition is cross-linked.

11.   A method for encapsulating a biological agent, said method comprising:
        combining said agent with a polymer according to any of the previous claims.

12.   The method according to Claim 11, wherein said biological agent is selected from the group consisting of: cells and pharmaceutically active compounds.

13.   The method according to Claim 11, wherein said polymer is a thermoreversible polymer.

14.   A method treating a host for a condition, said method comprising:
        administering to said host a polymeric composition comprising a polymer according to any of Claims 1 to 10.

15.   The method according to Claim 14, wherein said polymeric composition has a low melting point.

16.   The method according to Claim 14 or 15, wherein said polymeric composition further comprises a biologically active agent.

17.   A method for making a wound dressing, said method comprising combining a polymer according to any of Claims 1 to 10 with one or more blood derived agents to produce a composition and solidifying said composition.

18.   A method for preparing particles comprising an active agent, said method comprising:

dispersion said active agent in an encapsulation matrix comprising a cross-linkable
polymer;

producing particles of from said matrix;

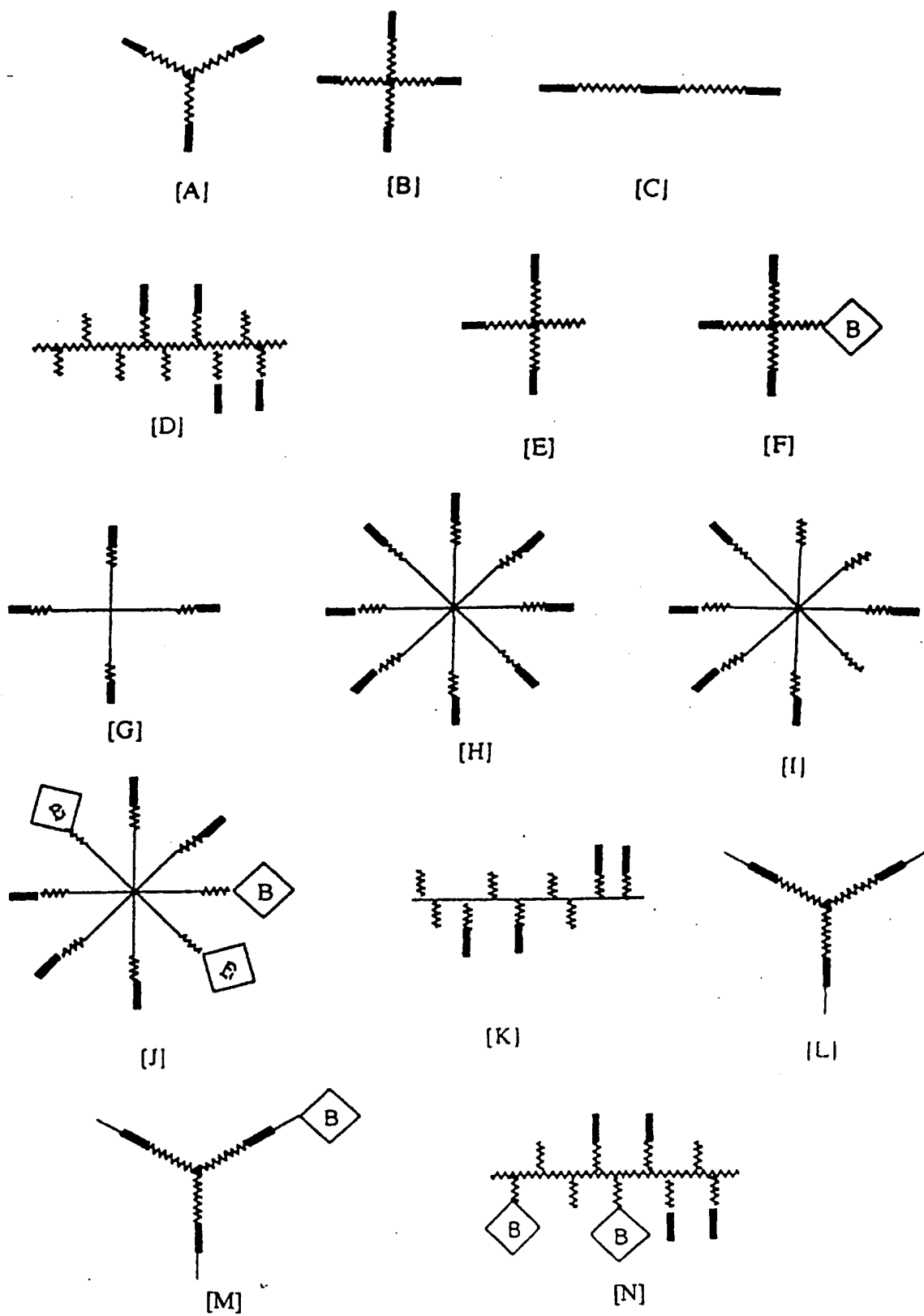and crosslinking said polymers of said particles.

5

19.   The method according to Claim 18, wherein said method further comprises
reducing the temperature of said particles prior to said crosslinking.

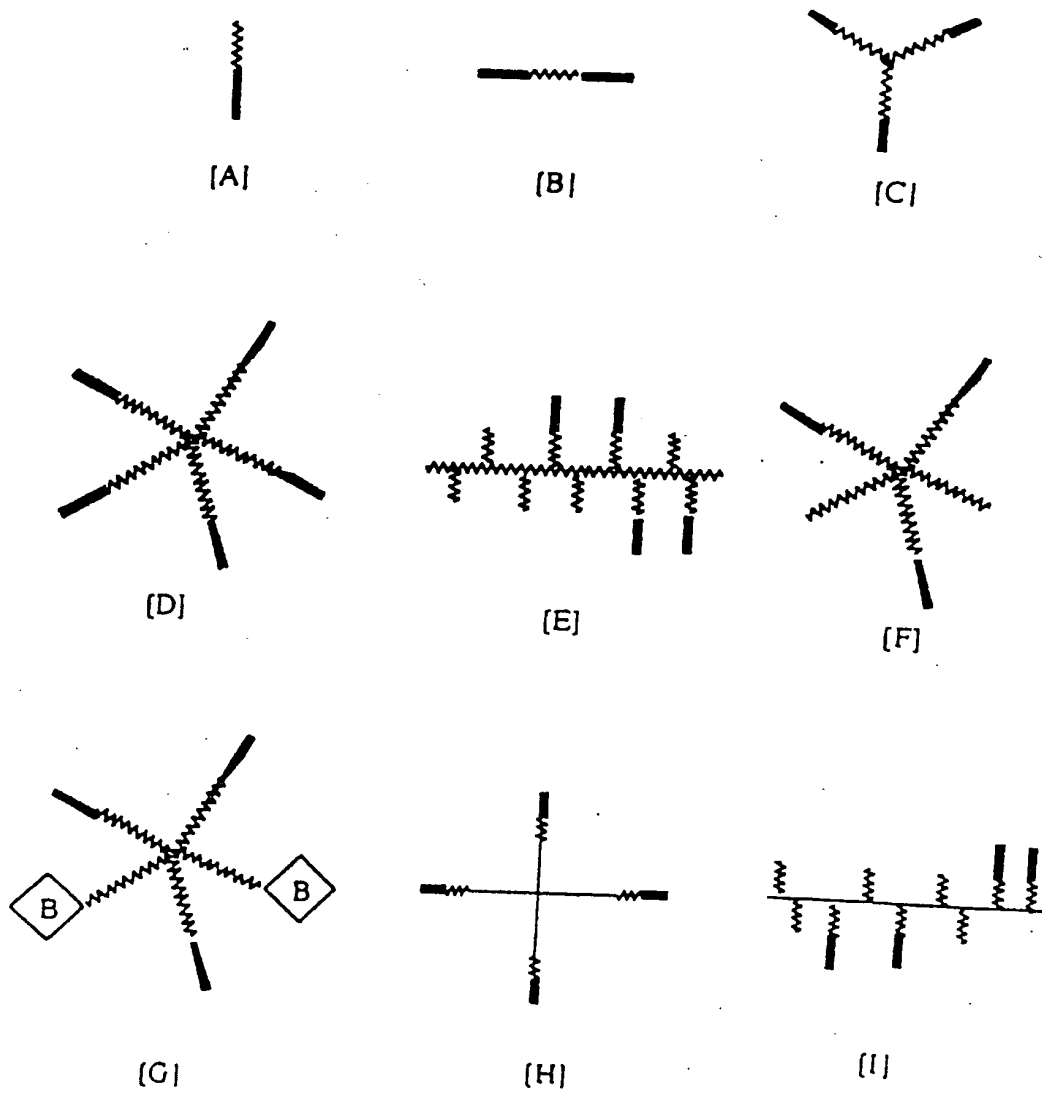20.   The method according to Claim 18, wherein said active agent is a drug.
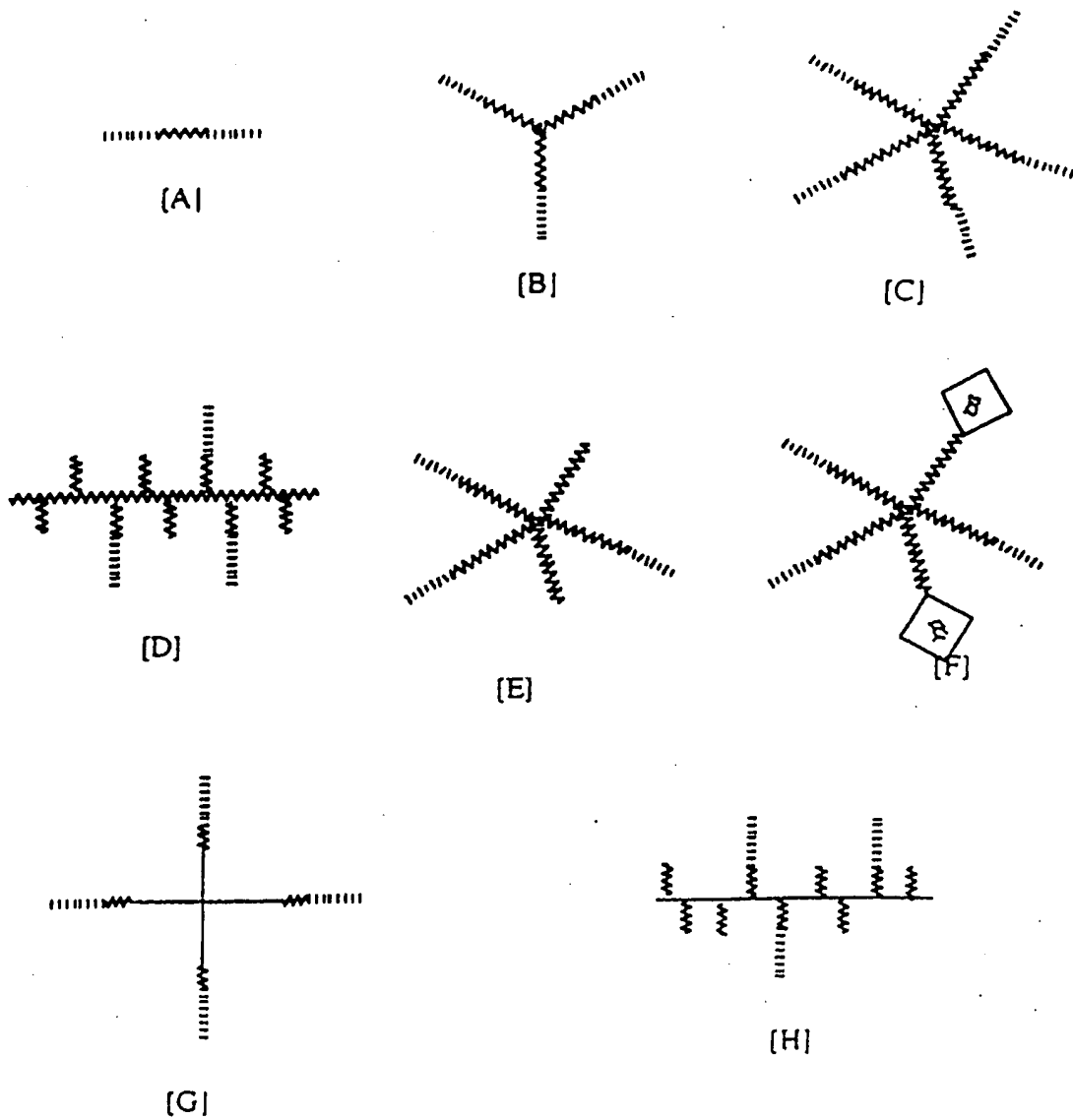
10

1/3

FIG. 1

[A] [B] [C]

[D] [E] [F]

[G] [H] [I]

[J] [K] [L]

[M] [N]

FIG. 2

[A]   [B]   [C]

[D]   [E]   [F]

[G]   [H]   [I]

FIG. 3

[A]

[B]

[C]

[D]

[E]

[F]

[G]

[H]

A.	CLASSIFICATION OF SUBJECT MATTER _; G_

IPC(6)   :A61F 2/00; A61K 9/14, 9/58; C086 63/08, 67/00

US CL   :514/772.4; 525/54.1, 54.2, 54.3; 530/810, 812, 815, 817

According to International Patent Classification (IPC) or to both national classification and IPC

B.	FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :   514/772.4; 525/54.1, 54.2, 54.3; 530/810, 812, 815, 817

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

  N/A

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

  N/A

C.	DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 5,410,016 A (HUBBELL ET AL) 25 April 1995, see entire document.	1,7 ---- 1-6
X	US 5,476,666 A (RHEE et al) 19 December 1995, see entire document.	1, 5-7

☐   Further documents are listed in the continuation of Box C.   ☐   See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
"O"	document referring to an oral disclosure, use, exhibition or other means	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 APRIL 1998	1 8 JUN 1998

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer
	NATHAN M. NUTTER
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0661

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/03020

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such
   an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-10
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

   Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
   1-10

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/03020

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I.   Claims 1-10, drawn to a biodegradable polymer classified in Class 525, subclass 54.1.

II.   Claims 11-13, drawn to a first method for encapsulating a biological agent classified in class 530, subclasses
       810+.

III.   Claims 14-16, drawn to a second method for treating a host classified in class 514, subclass 772.4.

IV.   Claim 17, drawn to a third method for making a wound dressing classified in class 602, subclass 48.

V.   Claims 18-20, drawn to a fourth method for preparing particulate encapsulated matrices classified in class 424,
       subclasses 489 plus.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT
Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

In the instant application the special technical feature, i.e., biodegradable region, and one of three photocondensable
regions, one hydrphobic end group and at least two hydrophilic end groups, has been shown not to be a contribution
over the art. See specifically US 5,410,016 A and US 5,476,666 A. Therefore, unity of invention is lacking between
groups I - V.

Form PCT/ISA/210 (extra sheet)(July 1992)*